## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Michael N. Sack | Senior Investigator and Branch Chief<br>Cardiovascular and Pulmonary Branch, NHLBI |

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Univ. of Witwatersrand Med. School, JHB, S. Africa | MBBCh | 1983-1988 | Medicine |
| Univ. of Witwatersrand Med. School, JHB, S. Africa | MSc | 1989-1990 | Hypertension |
| Georgetown University Med. Center, Washington DC | | 1991-1994 | Medical Residency |
| Washington Univ. in St. Louis Medical School | | 1994-1997 | Cardiology |
| Univ. of Cape Town Med. School, Cape Town, S. Afr. | Ph.D. | 1997-2000 | Molecular Biology |

### A. Personal Statement

I have a broad background in the molecular, cellular and biochemical biology of mitochondrial function and metabolism and investigate this biology in the context of disease pathophysiology. My focus on the regulatory control of mitochondrial function was initiated during my Cardiology Postdoctoral Fellowship at the University of Washington in St. Louis (1994-97) and has continued through my training and faculty positions at University College London, The University of Cape Town and at the NHLBI intramural program of the NIH since 2003. The overall research objectives in my laboratory are to understand how caloric levels modulate metabolism and mitochondrial function via the post-translational modification (PTM) of metabolic and mitochondrial proteins. The PTM's being explored are lysine residue acetylation and ubiquitination. These projects are briefly reviewed:

1. The modulation of mitochondrial proteins by acetylation/deacetylation is recognized as a major PTM in the control of mitochondrial function. Out laboratory is identifying and functionally characterizing novel intracellular quality control programs that are regulated by this PTM. We also interrogate the role of this nutrient sensing PTM in the modulation of immune function in humans.
2. To study the metabolic role of ubiquitination we are focusing on the E3-ubiquitin ligase Parkin. We became interested in this protein, as mutations in *PARK2,* the Parkin gene, gives rise to premature onset Parkinson Disease, and Parkin plays a pivotal role in mitochondrial quality control. Our initial study uncovered a novel role of Parkin showing that a pivotal function of this E3-ligase ubiquitinates and stabilizes the fatty acid transport protein CD36. The functional consequence of the deletion of Parkin includes resistance to fatty liver, insulin sensitivity and reduced fat accumulation during adipogenesis. A major goal of my laboratory is to delineate the mechanism whereby Parkin modulates lipid biology, mitochondrial homeostasis and stress susceptibility. The role of Parkin mutations in patients will also be explored in the context of lipid biology, insulin sensitivity, cardiac hypertrophy and mitochondrial homeostasis.

### B. Positions and Honors

POSITIONS:

- 1997- 2002 Senior Clinical Lecturer and Honorary Consultant - University College London Medical School and Middlesex Hospital, London, UK.
- 1998 - 2001 Assistant Professor, Department of Medicine, Director, Hatter Institute for Cardiology Research, Director, South African Medical Research Council Inter-University Cape Heart Group
- 2001 - 2002 Associate Professor, Department of Medicine, University of Cape Town, Director, Hatter Institute for Cardiology Research.
- 2000 - 2002 Director, South African Medical Research Council Inter-University Cape Heart Group
- 1998 - 2002 Physician: Cardiac Clinic - Groote Schuur Hospital, University of Cape Town Medical School
- 2003 - 2012 Investigator, Center for Molecular Medicine, NHBLI, NIH, Bethesda, MD

- 2012 - Senior Investigator, Center for Molecular Medicine, NHBLI, NIH, Bethesda, MD
- 2013 - Branch Chief, Cardiovascular and Pulmonary Branch

HONORS:

- Georgetown University Postgraduate Award - Original Research (Clinical Research) – 1993
- American College of Physicians (National Meeting) Award - Original Research as a Resident/Fellow -1994
- The Dudley P. Jackson Award for Consistent Research and Teaching by a Resident. American College of Physicians - Regional Chapter (Washington DC). -1994
- The Wesley Oler Award for The Outstanding Resident Physician. Georgetown University Medical Center - Internal Medicine Residency Program – 1994
- Howard Hughes Medical Institute Physician Postdoctoral Research Fellowship. 1995-1997
- Elected as Fellow - American College of Physicians / Am Society of Internal Medicine – 2000
- Ad-Hominum Promotion to Associate Professor of Medicine at Univ. of Cape Town – Sept. 2001
- Director, South African Medical Research Council Inter-University Heart Research Group 2000-02
- Elected member to the American Society for Clinical Investigation - 2009
- NHLBI Division of Intramural Orloff Award for Scientific Advancement for work on the Parkin protein - 2011
- Awarded Tenure at the NIH – 2012

## C. Selected Peer-Reviewed Publications (19 Selected from 87 publications)


1. McLeod CJ, Aziz A, Hoyt RF, McCoy JP, **Sack MN.** Uncoupling proteins 2 and 3 function in concert to augment tolerance to cardiac ischemia. *J. Biol. Chem*. 2005:280;33470-33476. PMID:16079144
2. Langenickel-Pagel I, Schwartz DR, Arena RA, Minerbi DC, Johnson DT, Waclawiw MS, Cannon RO, Balaban RS, Tripodi DJ, **Sack MN.** A discordance in rosiglitazone mediated insulin sensitization and skeletal muscle mitochondrial content/activity in type 2 diabetes mellitus. *Am J Physiol Heart Circ Physiol* 2007;293:H2659–H2666. PMCID: 17890427
3. Lynn EG, Mcleod, CJ, Gordon JP, Bao J, **Sack MN**. SIRT2 modulates anoxia-reoxygenation stress-tolerance in H9c2 cells via regulation of 14-3-3 ζ and BAD. *FEBS Letters.* 2008;582:2857-2862. PMCID:2566947
4. Langenickel-Pagel I, Bao J, Joseph JJ, Schwartz DR, Mantell BS, Xu X, Raghavachari N, **Sack MN.** PGC-1α integrates insulin signaling, mitochondrial regulation and bioenergetic function in skeletal muscle. *J. Biol. Chem.* 2008;283:22464-22472. PMCID:2504883
5. Lu, Z, **Sack MN.** ATF-1 is a hypoxia-responsive transcriptional activator of skeletal muscle uncoupling protein 3. *J. Biol. Chem.* 2008:283:23410-23418. PMCID:2517006
6. Lu Z, Scott I, Webster BR, **Sack MN.** The emerging characterization of lysine residue deacetylation on the modulation of mitochondrial function and cardiovascular biology. *Circ. Res*. 2009:105:830-841. PMCID:2766861
7. Bao J, Pang L, Lu, Z, Dimond C, Samsel L, McCoy JP, Leclerc M, Gius D, **Sack MN.** Characterization of the murine SIRT3 mitochondrial localization sequence and comparison of mitochondrial enrichment and deacetylase activity of long and short SIRT3 isoforms. *J. Cellular Biochemistry.*2010:110:238-247. PMCID:2858784
8. Bao J, Scott I, Lu Z, Pang L, Dimond C, Gius D, **Sack MN**. *SIRT3* is regulated by nutrient excess and modulates hepatic susceptibility to lipotoxicity. *Free Radical Biology and Medicine*. 2010:49:1230-1237. PMCID:20647045
9. Kendrick A, Choudhury M, Rahman SM, McCurdy CE, Bao J, Gius D, **Sack MN**, Friedman JE, Jonscher KR. Fatty liver is associated with reduced SIRT3 activity and mitochondrial protein hyperacetylation. *Biochemical J.* 2011;433:505-514. PMID: 21044047.
10. Liu H, Fergusson MM, Wu JJ, Rovira II, Liu J, Gavrilova O, Lu T, Bao J, **Sack MN**, Finkel T. Wnt signaling regulates hepatic metabolism. *Science Signaling*. 2011,4:ra6. PMCID: PMC3147298
11. Lu Z, Bourdi M, Li JH, Aponte AM, Chen Y, Lombard DB, Gucek M, Pohl LR, **Sack MN.** SIRT3-dependent deacetylation exacerbates acetaminophen hepatotoxicity. *EMBO Reports* 2011;12:840-846. PMCID: PMC3147261
12. Kim KY, Stevens MV, Rusk S, Huang RJ, Noguchi A, Springer D, Bocharov AV, Eggerman TL, Suen DF, Youle RJ, Amar M, Remaley AT, **Sack MN**. Parkin is a lipid-responsive regulator of fat uptake in mice and mutant human cells. *J.Clin. Invest.* 2011;121:3701-3712. PMCID: PMC3171101
13. Nguyen T, Stevens MV, Kohr M, Steenbergen C, **Sack MN**, Murphy E. Cysteine 203 of cyclophilin D is critical for cyclophilin D activation of the mitochondrial permeability transition pore. *J. Biol. Chem.* 2011;286:40184-92. PMCID: PMC3220546
14. Avila A, Huang RJ, Kim KY, Aponte AM, Tripodi D, **Sack MN.** Platelet mitochondrial dysfunction is evident in type 2 diabetes in association with modulation of mitochondrial anti-oxidant stress proteins. *Experimental and Clinical Endocrinology and Diabetes*. 2012;120:248-51. PMID:21922457
15. Scott I, Webster BR, Li JH, **Sack MN.** Identification of a molecular component of the mitochondrial acetyl transferase program: a novel role for GCN5L1. *Biochemical J.* 2012;443:655-61. PMID:22309213.

16. Webster BR, Scott I, Han, K, Li JH, Lu Z, Malide D, Chen Y, Samsel L, Connelly PS, Daniels MP, McCoy JP, Combs CA, Gucek M, **Sack MN**. Restricted mitochondrial protein acetylation initiates mitophagy. *J. Cell Science*. 2013;126:4843-4849.
17. Nguyen T, Wong R, Manazza S, Sun J, Chen Y, Wang G, Gucek M, Steenbergen C, **Sack MN**, Murphy E. Cyclophilin D modulates the mitochondrial acetylome. *Circ Res.* 2013;113:1308-1319.
18. Scott I, Webster BR, Chan CK, Okonkwo JU, Han K, **Sack MN**. GCN5-like protein 1 (GCN5L1) controls mitochondrial content through coordinated regulation of mitochondrial biogenesis and mitophagy. *J. Biol. Chem*. 2014*:*289;2864-72.
*19.* Lu Z, Chen Y, Aponte AM, Battaglia V, Gucek M, **Sack MN**. Prolonged Fasting Identifies Heat Shock Protein 10 as a Sirtuin 3 Substrate: Elucidating a New Mechanism Linking Mitochondrial Protein Acetylation to Fatty Acid Oxidation Enzyme Folding and Function*. J. Biol. Chem.* 2015;290:2466-76. doi: 10.1074/jbc.M114.606228.

## D. Research Support

NHLBI Intramural Research Program Funding:
**HL005102-06** Mitochondrial Biology in Cardiovascular Disease
**HL005199-04** Metabolic Regulation in the Pathophysiology of Diabetes
**HL006047-01** Acetylation in the Control of Mitochondrial Homeostasis

NIH Office of Rare Diseases:
**Bench to Bedside Award - Metabolic phenotyping of Parkin mutation associated Parkinson's Disease** -2012-13

Michael J. Fox Foundation:
**2014-2015 Parkin modulates neuroinflammation to sustain dopaminergic neuronal health**